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EXAMINER	
SKELDING, ZACHARY S	
ART UNIT	PAPER NUMBER
1644	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/676,045	ILAN ET AL.	
	Examiner	Art Unit	
	ZACHARY SKELDING	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 January 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,5-11,13,15-20,23-46,50-63,66-72,83-126 and 143-166* is/are pending in the application.

4a) Of the above claim(s) *See Continuation Sheet* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2,3,6-11,13,15,19,24,30-32,144-151,165 and 166* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Continuation of Disposition of Claims: Claims withdrawn from consideration are 1,5,16-18,20,23,25-29,33-46,50-63,66-72,83-126,143 and 152-164.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on January 11, 2010 has been entered.

   Claim 7 has been amended.

   Claims 4, 12, 14, 21, 22, 47-49, 64, 65, 73-82 and 127-142 have been canceled.

   Claims 1-3, 5-11, 13, 15-20, 23-46, 50-63, 66-72, 83-126 and 143-166 are pending.

   Claims 2, 3, 6-11, 13, 15, 19, 24, 30-32, 144-151, 165 and 166 are under consideration wherein the species of "immune-related or immune-mediated disorders or diseases" is "autoimmune liver disease" or "Crohn's disease"; the species of "culture conditions for the ex vivo education of NKT" includes "allogeneic antigens obtained from donors suffering from said immune-related or immune-mediated disease", "Kupffer cells" and "IL4".

   Claims 1, 5, 16-18, 20, 23, 25-29, 33-46, 50-63, 66-72, 83-126, 143, 152-164 have been withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected Group and/or species of invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on March 10, 2008.

   The previous rejections of record can be found in the Office Action mailed July 9, 2009.

2. The following is a quotation of the first paragraph of 35 U.S.C. 112:

   > The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 2, 3, 6-13, 15, 19, 24, 30-32, 144-151, 165 and 166 stand rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for the treatment of TNBS-induced-colitis in a first mouse in need of such treatment comprising: (1) orally administering to said first mouse colitis extracted proteins (CEP) prepared from colons that were removed from TNBS-induced-colitis mice, cut into small strips, mechanically homogenized, filtrated through a 40 mm nylon cell strainer, and the colitis extract supernatant separated from intact cells via centrifugation; (2) obtaining 0.5×10^6 liver associated lymphocytes and 2.5×10^6 splenocytes from a second mouse that had been treated with TNBS to induce colitis and had been orally administered CEP prepared as in step (1);

(3) adding to a culture of the 0.5 x 10^6 liver associated lymphocytes and 2.5 x 10^6 splenocytes from step (2) antigen presenting cells and CEP prepared as in step (1); (4) optionally adding to said culture IL4, IL10, TGFβ, IL18 or IL15, (5) administering the cultured cells of step (3) to the first mouse in need of such treatment to modulate the Th1/Th2 balance toward anti-inflammatory cytokine producing cells, resulting in an increase in the quantitative ratio between any one of IL4 and IL10 to IFNγ

does not reasonably provide enablement for

a method for the treatment of ***any*** immune-related or immune-mediated disorders or diseases in ***any*** mammalian subject in need of such treatment, by manipulating ***any or all*** NKT cell population(s) of said subject, wherein manipulation of said NKT cell population(s) results in modulation of the Th1/Th2 cell balance toward anti-inflammatory cytokine producing cells, said modulation being mediated by ***any*** components, cells, tissues or organs of said subject's or another subject's immune system, essentially for the reasons of record as put forth in the Office Action mailed September 9, 2008.

Applicant's augments

Applicant argues on pages 28-33 of their Remarks filed January 11, 2010 that the instant claims are enabled for a variety of reasons.

Applicant's arguments have been considered, but have not been found convincing, essentially for the reasons of record as put forth in the Office Action mailed July 9, 2009 as well as for the reasons set forth further below.

A. Ex vivo Education and the "IL10 to IFNγ ratio"

Discussing the data of Table 6 of the instant specification, applicant argues that because the increase in IL-10 levels versus baseline (+288) is greater than the increase in IFN-γ levels versus baseline (+38), "one of ordinary skill in the art would appreciate that the results…indicate that administration of antigen-exposed NKT cells will produce a beneficial result."

Applicant supports this conclusion with the following reasoning:

"The ratio represents an evaluation of IFN[γ] to insure that there is a "net profit" for anti-inflammatory responses (as judged by IL10 levels) compared to an induction of pro-inflammatory responses (as judged by IFNγ levels). Therefore, the change that that takes place by treatment via ex vivo exposure to antigens (education) indicates that although the IFNγ increased by 38 (38 in E"5 - 0 in E"2), this change was accompanied by an increase in IL10 of 288 (340 in E"5 - 52 in E"2). The directionality of the change was 288/38 in favor of IL10, i.e., a directionality that results in an increased anti-inflammatory response. The increased response was considered by the inventors to be beneficial, very similar to how E"3

showed an increase in IL10 (although without detection of an increase in IFNγ) by induction of oral toleration before isolation of the NKT cells. In essence, the inclusion of IFNγ in addition to IL10 is a control which insures that the measured effects are attributable to an anti-inflammatory directionality as opposed to a contemporaneous indiscriminate induction of equal or even higher levels of pro- inflammatory responses. These pro-inflammatory responses would negate beneficial responses otherwise provided by the induction of the anti-inflammatory responses."

(see Remarks, page 29, 1st paragraph).

Applicant's arguments have been considered, but have not been found convincing, essentially for the reasons of record as put forth in the Office Action mailed July 9, 2009.

The argument applicant puts forth above is essentially the same argument put forth by applicant in their previous remarks filed March 9, 2009 at page 28, 2nd paragraph to page 29, 1st paragraph.

This prior argument was not found convincing for the reasons put forth in the previous Office Action at page 4, 3rd-6th paragraphs, and for the reasons put forth below.

Applicant's argument continues to place emphasis on the teachings of the instant specification that:

"As shown by Table 6, culturing NK1.1+ T cells in the presence of disease associated antigens (subgroup E"5) leads to cytokine patterns that is similar to that of tolerized cells **as manifested by increase IL10 secretion**." (applicant's emphasis, see remarks page 29, 1st paragraph).

While the passage from the instant specification cited above is acknowledged, the teachings of the instant specification as a whole and the knowledge in the art collectively suggest the skilled artisan would not discount the increased IFNγ secretion and would consider the ratio of IL-10/IFNγ highly relevant to the use of the 'educated' cells in any future in vivo therapy.

For example, the working examples of the instant specification other than Example 7 report the value of the IL4 and IL10 to IFNγ ratio as a means of measuring the pro- or anti-inflammatory nature of NKT cells (see, e.g., Figures 2, 3, 5 and 9). This is consistent with the knowledge in the art where Th1/Th2 cytokine ratios are commonly measured (see, e.g., Zhou et al., J Clin Invest. 1998 Apr 15;101(8):1717-25, page 1722, Table III, cited herewith; Chiaramonte et al., Hepatology. 2001 Aug;34(2):273-82, page 276, right column, 1st paragraph, cited herewith).

Moreover, as stated in the previous Office Action at page 4, 5th paragraph, and still not addressed by applicant's argument, it is unclear how "the exact value of the IFNγ/IL10 is not important" when this is the very measure of treatment success recited, e.g., in claim 6: "c. re-

introducing to said subject the educated NKT cells obtained in step (b) which may modulate the Th1/Th2 cell balance toward anti-inflammatory cytokine producing cells, resulting in an increase in the quantitative ratio between any one of IL4 and IL10 to IFNγ."

B. The ex vivo educating Antigen

As to the use of any antigen related to/associated with an immune-related disorder to ex vivo educate NKT cells such that the educated NKT cells have the capability of modulating the Th1/Th2 cell balance toward anti-inflammatory cytokine producing cells, applicant argues (1) the skilled artisan need not know the "particular biomolecular constituent" of "colitis extracted protein" is responsible for mediating ex vivo education of NKT cells in order to practice the claimed method and (2) determining which extracts will be able to educate NKT cells "is merely a question of optimization."

Applicant's arguments have been considered, but have not been found convincing, essentially for the reasons of record as put forth in the Office Action mailed July 9, 2009.

Essentially as stated in the previous Office Actions, the sole attempt at demonstrating ex vivo education in the instant specification makes use of "colitis extracted protein" prepared by removing colons from TNBS-induced-colitis mice, cutting them into small strips, mechanically homogenizing them, then filtrating through a 40 mm nylon cell strainer, and separating the colitis extract supernatant from intact cells via centrifugation (see instant specification page 61, 3rd paragraph).

Assuming, arguendo, applicant could show the "colitis extracted protein" ex vivo educated NK1.1 T cells of Group E"5 from Table 6 of the instant specification were capable of treating colitis when re-introduced into the TNBS mouse from which they were initially obtained, such a finding would not be sufficient to enable the skilled artisan to practice the claimed method with the breadth of "educated" antigens encompassed by the instant claims.

This is because neither the instant specification nor the art seem to recognize what particular biomolecular constituent of the "colitis extracted protein," i.e., which epithelial cell or host microbial cell component, e.g., polypeptide and/or nucleic acid and/or lipid etc., is effecting NKT cells (see, e.g., Lee et al., Am J Gastroenterol. 2000 Apr;95(4):861, left column, 3rd paragraph and Kiron Das et al., Am J Gastroenterol. 2006 Dec;101(12):2889-90 and Margalit et al., Am J Gastroenterol. 2006 Dec;101(12):2890-91, in particular page 2890, right column, 2nd paragraph)(all cited previously).

Thus, the skilled artisan cannot extrapolate with any reasonable degree of predictability from the use of "colitis extracted proteins" as exemplified by the instant specification to the use of the genus of "colitis extracted proteins" made by any method, much less the use of any antigen associated with an immune-related disorder in the claimed methods.

To put it another way, while the skilled artisan need not know the "particular biomolecular constituent" (or constituents) of "colitis extracted protein" is/are responsible for mediating ex vivo education of NKT cells in order to practice the *enabled* embodiment of the claimed method put forth in the header to the instant Section, without any knowledge as to what constituent(s) is/are required for the NKT cells to be educated as claimed how is the skilled artisan to extrapolate these teachings to making use of any "allogeneic antigens obtained from donors suffering from…immune-related or immune-mediated disorder or disease" (claim 9) to ex vivo educate NKT cells or any "antigens or epitopes associated with said immune-related or immune-mediated disorder or disease to be treated, antigens or epitopes associated with the immune-mediated inflammatory response, or any combination thereof" (claim 7) to educate NKT cells without resorting to undue experimentation?

As to applicant's second argument about "optimization", this is not found convincing because first and foremost, the instant specification fails to teach the skilled artisan how to practice the claimed invention with any "allogeneic antigens obtained from donors suffering from…immune-related or immune-mediated disorder or disease" (claim 9) or any "antigens or epitopes associated with said immune-related or immune-mediated disorder or disease to be treated, antigens or epitopes associated with the immune-mediated inflammatory response, or any combination thereof."

Thus, any argument about how the skilled artisan may be able to routinely optimize a not enabled educating extract of antigens is a moot point.

However, it is worth noting that applicant has missed the main point of this aspect of the previous rejection which is that there are a vast multitude of different ways that the skilled artisan could imagine preparing an cellular extract, e.g., by any method or combination of methods involving mild detergent or strong detergent or hypotonic lysis or acid lysis or sonication or French press or boiling or freeze/thawing, etc...with the further variation of soluble and insoluble fractions, ALL of which would be expected by the skilled artisan to give a different spectrum of materials that would be expected to have varying abilities to ex vivo educate NKT cells in a pro- or anti-inflammatory direction or having no effect at all. Yet the skilled artisan would have no clue which, if any of these extracts could be used as claimed.

Moreover, without knowledge of what antigen(s) is/are capable of ex vivo educating NKT cells as claimed, the skilled artisan would have little hope of reliably predicting if any particular disease can even be a source of epitope or antigen that can be used in the claimed method.

For example, consider the immune-related disorder psoriasis. Some antigens or epitopes known to be associated with this disease are K13, hnRNP A1 and FLJ00294 (see Jones et al., J Invest Dermatol. 2004 Jul;123(1):93-100, in particular page 98, cited herewith). However, none of these antigens were/are known to stimulate NKT cells, and there is no expectation in the art that they would do so because these ligands were not known to bind CD1d, and would

have been considered just as unlikely as any other randomly chosen polypeptide to activate CD1d-independent NKT (see, e.g., Godfrey et al., Immunol Today. 2000 Nov;21(11):573-83, in particular page 577, left column, 2nd-3rd paragraphs, cited previously).

Thus, this example illustrates how the skilled artisan would not know how to proceed to practice the claimed invention with a reasonable degree of predictability for any given disease, e.g., psoriasis.

C. Extrapolating from murine to human NKT cells and unpredictability in the art of NKT cells in general

Applicant argues "the use of 'murine NKT 1.1 T cells' or 'routine TNBS colitis,' as described in the specification, should not limit one to extrapolate that similar effects may be achieved with human NKT cells. Murine NKT cells are considered by one of skill in the art to be an acceptable model to study the immunological effects that would occur in human NKT cells. The large amount of research devoted to such studies would have been impossible without this model. Similarly, the TNBS colitis model is widely used as an animal model of human colitis. The availability this model as a research tool is possible because of its ability to be adapted to human disease processes - there is no particular utility or desire among researchers for curing colitis conditions in mice. The use of animal models for the study and experimentation of processes and the development of proof of principles in therapeutic procedures for humans is a time honored method of practice for research as well as for clinical trials."

Applicant's arguments have been considered but have not been found convincing.

First, the reliability of the TNBS model as it pertains to human colitis was not a matter of concern in the rejections of record. Rather, the issue was can the skilled artisan extrapolate results obtained using murine NKT cells in a mouse to the use of human NKT cells in a human with any reasonable degree of predictability?

Applicant asserts "Murine NKT cells are considered by one of skill in the art to be an acceptable model to study the immunological effects that would occur in human NKT cells" but provides no data to counter the objective evidence put forth in the prior Office Actions that the differences in the biological activity and physiology of human and mice NKT cells as a whole far exceeds their similarities which makes extrapolating from one to the other an unpredictable endeavor (see, e.g., the Office Action mailed September 9, 2009 at page 12, last paragraph to page 13-14 bridging paragraph). In this regard it is noted that arguments of counsel cannot take the place of factually supported objective evidence. See, e.g., *In re Huang*, 100 F.3d 135, 139-40, 40 USPQ2d 1685, 1689 (Fed. Cir. 1996); *In re De Blauwe*, 736 F.2d 699, 705, 222 USPQ 191, 196 (Fed. Cir. 1984).

Furthermore, in the paragraph bridging pages 31-32 of their remarks applicant makes a number of assertions and arguments which seem to be based on the premise that because

some of the rejected claims recite "obtaining NKT cells" as the first step, but do not specify any particular sub-population of NKT cells to be obtained, the previous rejection of record is not applicable to the instant claims. Along these lines applicant further argues, "…under the Examiner's interpretation, the Doherty and Kaneko references would teach that the anti-inflammatory results achieved by the inventor would be unachievable. Reconciliation of this statement with the results describe in the specification is possible by the conclusion that results of subpopulations do not predict results of the population as a whole."

While it is true that some of the instant claims are directed to manipulating the genus of NKT cells ex vivo followed by administration to the subject to be treated, the sole "working example" of the instant specification, i.e., Example 7 on pages 79-86, was carried out with a particular *sub-population* of NKT cells, murine CD3+ NK1.1+ NKT cells (see the Office Action mailed September 9, 2009 at page 12, 2nd and 3rd paragraphs). Moreover, as described by the Kronenberg and Doherty publications, the various sub-populations of murine and human NKT cells which share homologous Vα chains, such as murine Vα14i and human Vα24i NKT cells, have great differences in their biologic activities.

Thus, the skilled artisan would have substantial uncertainty about their ability to extrapolate the function of a given sub-population of NKT cells from one organism to the next, and even greater uncertainty about the likely effect of ex vivo "educating" the genus of NKT cells and administering them to a subject having autoimmune liver disease or Crohn's disease.

Furthermore, as described in the previous Office Action with the teachings of the Kronenberg and Doherty publications, when an NKT cell is put into an animal the results are often unpredictable. This ability of NKT cells to have both pro- and anti-inflammatory activities in often unpredictable ways is referred to in the art as NKT cell "plasticity," and is thought to be a function of the cells themselves and/or their interaction with their environment. For example, well after applicant's date of invention one of the inventors of the instant application teaches the following about NKT cell plasticity:

"NKT cells have been shown to be remarkably versatile in function during various immune responses [22]. This subset of lymphocytes has diverse influences in various disease models and a unique ability to suppress or enhance immunity in different microenvironments [1]. The term 'plasticity' is sometimes used to describe their function. NKT plasticity may require a duality in function, such as a capability for both Th1 and Th2 cytokine secretion in different immune backgrounds. Whether or not this plasticity is mediated by a ligand still remains unclear. ***NKT plasticity may evolve from the use of different ligands or from different signals in the immune microenvironment [23]. The same ligand can generate different types of immune responses by NKT cells in different microenvironments. In light of the differing effects of a given ligand in vivo and in vitro, the net effect of NKT activation may not result from the binding of a single ligand, but rather from the sum of the effects of a variety of mediators*** [3,17]. It may also depend on cell–cell interaction or on the influence of cytokines or co-stimulatory molecules. The DC–NKT and/or NKT–Tregs cross-talk may be of importance in determining NKT plasticity [7,24,25]. ***Organ-specific***

factors also play a role in NKT plasticity, with different responses generated in different organs by an identical stimulus. Antigen presentation and APCs may play an important role under these conditions [26]. Originally identical stimuli may reach NKT cells via different pathways through presentation by different APCs [1,27]. ***On the other hand, plasticity may result from the natural programmes of different subsets of cells*** [28]. ***NKT cells are a heterogeneous population of lymphocytes that can differ in their CD1d reactivity and CD expression***. Apart from inherent heterogeneity between different NKT populations, alterations in cellular membranes with altered lipid raft properties can affect raft-bound receptors, such as CD1d, and may add to the variety of responses [29,30]. Distinct NKT cell subsets have been suggested to play positive and negative regulatory roles and to define a new immunoregulatory axis, with broad implications for tumor immunity and other immunological and disease settings [31]. ***For NKT cells, it is unclear as yet whether their extensive functional capacities can be attributed to a single population that is sensitive to environmental cues or if functionally distinct NKT cell subpopulations exist*** [22]. Thus, NKT plasticity may be considered the result of several of the above-mentioned factors, with CD1d-dependent ligands being the final link in a chain of factors that determines the end response [30,32]."

(see Yaron Ilan, Clinical and Experimental Immunology, 158: 300–307, 2009, at page 301, emphasis added, cited herewith).

Thus, given the uncertainty in the art as to what controls the in vivo pro- or anti-inflammatory activities of NKT cells well after applicant's date of invention it is unclear how the skilled artisan would have had any reasonable degree of certainty of practicing the claimed invention as of applicant's date of invention.

Moreover, it is noted that applicant has not adequately addressed the uncertainty of treating autoimmune liver disease with NKT cells that favor the production of IL-4 given the teachings of Kaneko that Con-A activated Vα14 NKT cells which over-produce IL-4 induce hepatitis by killing liver cells. Thus, why would the skilled artisan consider treating autoimmune liver disease with NKT cells that favor the production of IL-4 a predictable endeavor?

D. NKT 1.1+ T cells vs. CD56+ T cells

The instant claims encompass in their breadth methods of manipulating the NKT cell population in humans to treat immune-related disorders wherein the particular subtype of NKT cells used for the ex vivo education step is human CD56+ NKT cells (see, e.g., claim 32).

The instant specification provides a single working example of obtaining NKT cells, in particular, CD3+ NK1.1+ NKT cells from a mouse and *ex vivo* "educating" the NKT cells in the presence of colitis extracted proteins (CEP) obtained from a mouse with TNBS induced colitis, see Example 7.

To put the murine NK1.1+ T cells of Example 7 of the instant specification and the human CD56+ NKT cells of, e.g., claim 126, into the context of the knowledge in the art it is helpful to describe how these T cell subtypes fits into the genus of NKT cells.

The NKT cell genus encompasses subtypes with differing cell surface markers, differing antigen-presenting molecule restriction specificities, and in turn differing modes of activation and differing effector functions. (See, for example, Kronenberg et al., Nat Rev Immunol. 2002 Aug;2(8):557-68, especially page 557 to page 558, left column and Table 1, cited previously).

For example, 'classical' murine NKT cells express the invariant T cell receptor Vα14-Jα18/Vβ8.2, Vβ7 or Vβ2 (referred to as 'Vα14i' NKT cells by Kronenberg). Murine Vα14i cells, via their invariant αβ T cell receptor, recognize an antigen bound to a β2-microglobulin-associated nonpolymorphic, nonclassical CD1d MHC molecule. As of applicant's date of invention, physiologically relevant, naturally auto- or allo- antigens recognized by murine Vα14i NKT cells were unknown (however a 'naturally' occurring small molecule isolated from a marine sponge, α-galcer, was known in the art to be a CD1d binding molecule that is recognized by murine Vα14i NKT cells in the context of CD1d and potently activates said cells in the presence of appropriate costimulatory signals, see Kronenberg, page 557, left column, 2nd paragraph and Box 1 'invasion of the murine sponges?').

With respect to humans, the equivalent of murine Vα14i NKT cells are 'Vα24i' NKT cells which are similar to the murine cells in that they have a very restricted TCR repertoire and in that they recognize marine sponge α-galcer bound to CD1d (see Kronenberg, ibid).

However, there are significant differences between the biology of human and mouse NKT cells, particularly human CD56+ NKT cells, that make extrapolation from murine NK 1.1 T cells to human CD56+ T cells highly unpredictable.

For example, Doherty et al., Immunol Rev. 2000 Apr;174:5-20 (cited previously) teaches at page 10, left col., 1st paragraph through page 11, emphasis added: 'Studies in humans have also identified NKT-cell populations that co-express αβ or γδ TCRs and various NK receptors, including CD16, CD56, CD69, CD161, KIR receptors and/or CD94 (46–49). NKT cells account for about one third of all hepatic T cells but about 2% of peripheral T cells (4, 8, 9, 33). ***They include a human NK1.1+ T-cell homolog that expresses a TCR that is almost identical to the murine Vα14Jα281 TCR chain, Vα24JαQ (41). However, while Vα14Jα281 TCR expressing NK1.1+ T cells account for about 40% of all hepatic T cells in mice, the human Vα24JαQ TCR is present on a very small percentage of both peripheral and hepatic T cells (8). Therefore, while murine NKT cells represent a homologous population of T cells that express NK1.1 and a Vα14Jα281 TCR, human NKT cells constitute a heterologous population of T cells expressing various TCRs and NK receptors.*** Several phenotypic definitions of human NKT cells, based on co-expression of a

CD3/TCR complex and either CD16, CD56, CD161 or NK receptors for class I, have been proposed (8, 33). We have found that the co-expression of CD3 and CD56 serves best to define NKT cells that are characteristic of the human liver ***(Table 2). This NKT phenotype is most strikingly associated with the liver, and the expression of CD56 by hepatic T cells correlates with the expression of other NK markers and the ability of T cells to mediate NK cytolytic functions. We therefore have defined CD3+CD56+ cells in the human liver as 'hepatic natural T (NT) cells' (8). The majority of hepatic NT cells and other NKT cells express the CD8 co-receptor*** but CD4+ and DN cells are also present. In our studies of normal donor tissue, ***up to 35% of hepatic CD3+CD56+ (NT) cells were found to express γδ TCRs*** (4, 8). Ishihara et al. (33) reported that only 10% of hepatic CD3+CD161+ cells express this TCR isotype. However, six of the seven specimens in the latter study were from hepatectomy procedures performed for hepatic malignancy. The presence of a tumor may significantly influence the local repertoire of T-cell phenotypes. Both we (8) and Ishihara et al. (33) noted that large proportions of hepatic NT and other NKT cells express mature and activated phenotypes in tissue samples from both normal and malignant livers. This suggests that they are actively involved in local immune responses in the liver...A major role for human hepatic NKT cells may be to influence the local immunological milieu through the production of cytokines. In two studies, intracellular staining and flow cytometry were used to detect cytokine production by lymphocyte subsets from normal (9) and hepatitis C virus (HCV)- infected (32) livers. These studies showed that hepatic NT cells, as well as hepatic T cells and NK cells, can produce the inflammatory cytokines IFN-γ and TNF-α upon pharmacological stimulation or CD3 cross-linking (Fig. 7). The inflammatory cytokine IL-2 is also produced by significant proportions of hepatic NT cells and T cells, and a smaller proportion of hepatic NT cells (mean 15%) produce the Th2/Tc2 cytokine IL-4. ***As stated above, the predominance of Th1/Tc1 cytokine production by hepatic lymphocytes may reflect the production of proinflammatory cytokines by hepatocytes and Kupffer cells (30, 31) and suggests that the normal liver harbors an inflammatory environment that may be indicative of ongoing immune activity.*** IFN-γ and IL-4 can also be produced by murine NK1.1+ T cells (39, 40). ***These cells are predominantly IL-4 producers, suggesting that the majority of hepatic NT cells are either functionally distinct from murine NK1.1+ T cells or are polarized by the liver to produce predominantly Th1/Tc1 cytokines*** ."

Thus, the skilled artisan would consider extrapolating results from murine NK 1.1+ T cells to human CD56+ NK T cells an unpredictable endeavor.

E. Methods further comprising orally administering components, cells, tissues and/or organs…

The instant claims include a method of ex vivo educating NKT cells and administering the educated cells to a patient "***further comprising the step*** of eliciting in said subject immune modulation of said immune-related or immune-mediated disorder or disease by ***administering to said subject components, cells, tissues and/or organs derived from any allogeneic donor suffering from said immune-related or immune-mediated disorder, xenogeneic sources, syngeneic sources, autologous sources, non-autologous sources,***

immunologically functional equivalents, or any combination thereof, wherein said components, cells, tissues or organs are administered ***orally***. (see, e.g., claim 15)

Applicant continues to make arguments concerning the teachings of Margalit and says that they "properly supports a proof of principle and that the inventors were in possession of the invention." Applicant also argues that some experimentation is permissible so long as it is not undue.

Applicant's argument has been considered has not been found convincing because as put forth in the previous Office Action at page 8, 3rd paragraph:

"[a]pplicant's argument appears to be based on the teachings of Margalit, Am J Gastroenterol. 2006 Mar;101(3):561-8 as well as Hyun and Barrett, 2006 Am J Gastroenterol 101; 569-571 and yet applicant has provided copies of the abstracts for these articles but not the articles themselves. Thus, the teachings of the reference as a whole cannot be properly evaluated.

Moreover, even if 'Margalit et al. (Am J Gastroenterol. 2006 Mar;101(3):561-8) teaches some moderate success in treating Crohn's disease with orally administered autologous extract prepared from colon biopsies removed from patients receiving a colonoscopy' as asserted by applicant (noting that the Margalit Abstract supplied by applicant teaches 'oral administration of Alequel™ is a safe method for treatment of…CD…***its efficacy needs to be proven***'(emphasis added)), this would not convincingly demonstrate that the disclosure of the instant specification enables the enormous breadth of the claimed invention as put forth four paragraphs above.

This is because the prior art teaches a number of large, rigorous and definitive clinical trials and failures of oral antigen immunotherapy as taught by Pozzilli and Wiendl (see the previous Office Action paragraph bridging pages 11-12). Thus, the field of oral antigen immunotherapy is at best highly unpredictable and at worst totally unsuccessful."

Applicant's arguments still do not convincingly address these issues.

In conclusion, when Applicant's arguments and the evidence of the instant specification are taken as a whole and weighed against the evidence supporting the *prima facie* case of unpatentability, the instant claims, by a preponderance of evidence, remain unpatentable. See M.P.E.P. § 716.01(d).

4. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

5. Claims 2, 3, 6-11, 13, 15, 19, 32, 144-151, 165 and 166 stand rejected under 35 U.S.C. 102(b) as being anticipated by Ilan Yaron (WO 02051986, cited on an IDS), essentially for the reasons of record as put forth in the Office Action mailed July 9, 2009.

Applicant argues the instant application is entitled to the benefit of prior filed application 10/451,881 which has an effective filing date of December 24, 2001 and thus WO 02051986 is not prior art.

Applicant's argument is not found convincing because if applicant desires to claim the benefit of a prior-filed application under 35 U.S.C. 120, 121 or 365(c), a specific reference to the prior-filed application in compliance with 37 CFR 1.78(a) must be included in the first sentence(s) of the specification following the title or in an application data sheet. For benefit claims under 35 U.S.C. 120, 121 or 365(c), the reference must include the relationship (i.e., continuation, divisional, or continuation-in-part) of the applications.

If the instant application is a utility or plant application filed under 35 U.S.C. 111(a) on or after November 29, 2000, the specific reference must be submitted during the pendency of the application and within the later of four months from the actual filing date of the application or sixteen months from the filing date of the prior application. If the application is a utility or plant application which entered the national stage from an international application filed on or after November 29, 2000, after compliance with 35 U.S.C. 371, the specific reference must be submitted during the pendency of the application and within the later of four months from the date on which the national stage commenced under 35 U.S.C. 371(b) or (f) or sixteen months from the filing date of the prior application. See 37 CFR 1.78(a)(2)(ii) and (a)(5)(ii). This time period is not extendable and a failure to submit the reference required by 35 U.S.C. 119(e) and/or 120, where applicable, within this time period is considered a waiver of any benefit of such prior application(s) under 35 U.S.C. 119(e), 120, 121 and 365(c). A benefit claim filed after the required time period may be accepted if it is accompanied by a grantable petition to accept an unintentionally delayed benefit claim under 35 U.S.C. 119(e), 120, 121 and 365(c). The petition must be accompanied by (1) the reference required by 35 U.S.C. 120 or 119(e) and 37 CFR 1.78(a)(2) or (a)(5) to the prior application (unless previously submitted), (2) a surcharge under 37 CFR 1.17(t), and (3) a statement that the entire delay between the date the claim was due under 37 CFR 1.78(a)(2) or (a)(5) and the date the claim was filed was unintentional. The Director may require additional information where there is a question whether the delay was unintentional. The petition should be addressed to: Mail Stop Petition, Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450.

If the reference to the prior application was previously submitted within the time period set forth in 37 CFR 1.78(a), but not in the first sentence(s) of the specification or an application data sheet (ADS) as required by 37 CFR 1.78(a) (e.g., if the reference was submitted in an

oath or declaration or the application transmittal letter), and the information concerning the benefit claim was recognized by the Office as shown by its inclusion on the first filing receipt, the petition under 37 CFR 1.78(a) and the surcharge under 37 CFR 1.17(t) are not required. Applicant is still required to submit the reference in compliance with 37 CFR 1.78(a) by filing an amendment to the first sentence(s) of the specification or an ADS. See MPEP § 201.11.

Thus, Ilan Yaron continues to anticipate the instant claims.

6. No claim is allowed.

7. Any inquiry concerning this communication or earlier communications from the examiner should be directed to ZACHARY SKELDING whose telephone number is (571)272-9033. The examiner can normally be reached on Monday - Friday 8:00 a.m. - 5:00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on 571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Zachary Skelding/
Examiner, Art Unit 1644